ORIGINAL RESEARCH PAPER

Preventive Medicine

UNDERSTANDING THE COMPLEXITIES OF IRON METABOLISM AND ASSESSMENT FOR EFFECTIVE PRIMARY PREVENTION OF IRON DEFICIENCY ANEMIA

KEY WORDS: Iron Metabolism, Iron Deficiency Anemia, Hepcidin, Prevention of IDA, Nutrition Education

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ABSTRACT

Iron deficiency anemia (IDA) is a widespread nutritional disorder affecting individuals globally. This article elucidates the complexities of iron metabolism, regulation, and assessment, highlighting the crucial role of hepcidin in iron homeostasis. The clinical manifestations, risk factors, and diagnostic markers of IDA, including serum ferritin, transferrin saturation, and emerging markers like erythroferrone are discussed. Effective prevention strategies, such as promoting healthy feeding practices, iron-fortified foods and drinks, and nutrition education, are emphasized. Early detection and management of IDA are critical to mitigating its adverse effects on cognitive function, physical performance, and overall well-being. This review aims to provide healthcare providers with a comprehensive understanding of iron metabolism and primary preventive strategies of IDA.

INTRODUCTION

Iron (Fe) is an essential element involved in a variety of vital functions, required for --

- Synthesis of haemoglobin,
- Cell growth and differentiation,
- Deoxyribonucleic acid synthesis,
- Neurotransmission,
- Immunity,
- Cardiopulmonary function,
- Oxygen transport and
- Cellular respiration.[1,2]

Iron Distribution And Content In The Body

Total body iron content: Approximately 3 to 4 g.
Erythron (erythrocytes and their precursors): Approximately 2–3 g (mostly in hemoglobin).
Hepatocytes: Up to 1 g (in its cytoplasmic ferritin).
The plasma iron pool: 3–4 mg.[1,2]

Daily Iron Demand And Recycling

Daily iron demand for erythropoiesis and for other tissues: 20–25 mg.
Daily iron recycled by macrophages: 20–25 mg. (upon phagocytosis of erythrocytes).[1,2]

Iron Loss

Basal Loss: 1 to 2 mg / day
Menstrual Loss: Additional 1 mg / day.[1,2]

Iron Absorption And Transport

Iron Acquisition

Dietary Iron: Iron is primarily obtained from the diet in two forms: heme iron (from meat) and non-heme iron (from plant-based foods).

Heme Iron Absorption: Heme iron is more readily absorbed than non-heme iron.

Non-heme Iron Reduction: Non-heme iron (Fe3+) must be reduced to Fe2+ by a reductase enzyme before it can be absorbed.

Non-heme Iron Transport: The reduced Fe2+ is then transported across the intestinal cell membrane by a protein called DMT1 (divalent metal transporter 1)[1,2]

Iron Transport and Storage

Intracellular Iron: Once inside the intestinal cell, iron can be stored in a protein called ferritin or exported into the bloodstream.

Iron Export: The iron exporter protein ferroportin transports iron from the intestinal cell into the bloodstream.

Transferrin Binding: Iron in the bloodstream binds to a protein called transferrin, which carries it to cells throughout the body.

Cellular Iron Uptake: Cells take up iron by binding to transferrin and internalizing it through a process called receptor-mediated endocytosis.[1,2]

Key Factors In Iron Metabolism

DMT1: A protein that transports iron into cells.
Ferritin: A protein that stores iron in cells.
Ferroportin: A protein that exports iron from cells.
Transferrin: A protein that transports iron in the bloodstream.[1,2]

Regulation Of Iron Absorption

In humans, there is no regulated excretion of iron thus the iron balance is primarily controlled at the level of intestinal absorption that takes place in the proximal portion of the duodenum. Under physiological conditions, intestinal iron absorption is controlled primarily by body iron content and erythropoiesis. Specifically, iron uptake can be enhanced in the case of high erythropoietic demand or suppressed when iron stores are repleted. Only 1–2 mg of iron is absorbed daily in the gut, which is equivalent to the daily loss[1,2]

Hepcidin: The Iron Regulator

Hepcidin, a hormone produced by the liver, plays a crucial role in regulating iron levels in the body. It does this by controlling the release of iron from cells, particularly in the intestines and macrophages.

How Hepcidin Works?

Blocking Iron Export: Hepcidin binds to a protein called ferroportin, which is responsible for exporting iron from cells. When hepcidin binds to ferroportin, it causes the ferroportin to be degraded, effectively reducing the amount of iron that can be released into the bloodstream.

Influencing Iron Absorption: Hepcidin also influences the absorption of iron from the diet by regulating the expression of iron transporters in the intestines.

Factors Affecting Hepcidin Levels

Iron Levels: When iron levels are high, hepcidin production increases to reduce iron absorption and release.

Inflammation: Inflammatory conditions can also stimulate hepcidin production, leading to decreased iron availability. High hepcidin levels are associated with inflammatory conditions, such as cancer, chronic infections, and chronic kidney disease, and lead to anemia of inflammation.

Erythropoiesis: During periods of increased red blood cell production, hepcidin levels decrease to ensure adequate iron supply.

Matriptase-2: This liver protein inhibits hepcidin production, leading to increased iron absorption.

Erythroferrone: This hormone, produced by erythroid cells, also inhibits hepcidin, promoting iron release.

Ferroportin And Hepcidin In Iron Homeostasis

Hepcidin Binding: When hepcidin levels are high, it binds to ferroportin.

Ferroportin Degradation: This binding triggers the internalization and degradation of ferroportin, reducing the amount of iron that can be exported from cells.

Clinical Manifestations Of Iron Deficiency And Ida

Iron deficiency is considered the most common nutritional deficiency leading to anemia.[3] Iron deficiency (ID) is one of the most common micronutrient deficiencies and a common global health issue. Iron deficiency, can lead to a wide range of clinical manifestations, occurs as a spectrum, ranging from iron depletion without anemia to impaired erythropoiesis and anemia. ID particularly affects cognitive function, physical performance, and overall well-being.

Iron deficiency can result in

- Severe fatigue,
- Reduced exercise capacity,
- Poor work performance,
- Ridged/brittle nails,
- Hair loss,
- Aching and restless legs syndrome
- Anxiety, low mood/depression,
- Cognitive decline or learning disabilities
- Poor concentration,
- Malnutrition,
- Alopecia,
- Pica – a craving and purposive consumption for non-food items such as ice (pagophagia) and starch (amylophagia) may develop, especially in women whose serum ferritin < 10 µg / L
- Iron deficiency and anaemia during pregnancy are associated with adverse maternal and fetal outcomes. Children born to mothers with iron deficiency display neurocognitive deficits leading to learning and memory impairments that persist into adulthood.
- Postpartum anaemia is associated with depression, high levels of fatigue, poor cognition and difficulties with breast feeding.
- Pallor of the skin, conjunctivae, and nail bed is one of the most recognized signs of IDA. Hence presence of pallor in women should prompt the clinician to assess anemia and iron status, and consider the diagnosis of IDA. [1,4,5]

Risk Factors

Individuals At Risk Of Developing Iron-deficiency Anemia Include

- **Those with high iron requirements:**
- Infants
- Preschool children
- Adolescents
- Young menstruating women
- Pregnant and postpartum women

- **Female Endurance Athletes:**
- Increased hepcidin expression, hemolysis, and sweating associated with exercise can contribute to iron deficiency.

- **Obese Women:**
- Obesity-related inflammation can increase hepcidin expression, reducing iron absorption.

- **Other Healthy Women:**
- Vegetarians/vegans
- Blood donors

- **Women With:**
- Teenage pregnancy
- Previous anemia
- Multiple gestation
- Short inter-pregnancy interval (< 1 year) [1]

Assessment Of Iron Status

Ferritin: A Measure of Iron Stores

Ferritin is a protein that stores iron within cells. Low levels of ferritin in the blood often indicate low iron stores. However, it's important to note that ferritin levels can be influenced by factors other than iron, such as inflammation.[2] Ferritin is the best indicator of iron deficiency and a low ferritin alone is diagnostic of IDA. In presence of infection, malignancy or chronic inflammation, the ferritin rises as it is an acute phase protein. [4]

Normal Iron Stores

A serum ferritin level between 100 and 300 µg/L typically indicates adequate iron stores, especially in the absence of inflammation or other health conditions.

Iron Deficiency

A serum ferritin level below 30 µg/L is a strong indicator of iron deficiency, particularly when inflammation is not a factor. WHO recommends serum ferritin cutoff of <15 g/L for pregnant women in their first trimester, but with no thresholds proposed for the second or third trimester of pregnancy. Recent guidance by the British Society for Haematology (BSH) and the American College of Obstetricians and Gynecologists proposed a higher threshold of <30 g/L to indicate ID during pregnancy. [4]

Inflammation

In inflammatory conditions, ferritin levels can be elevated, making it a less reliable marker of iron stores. In such cases, a lower ferritin level, around 100 µg/L, may still indicate iron deficiency.

WHO Guidelines

The World Health Organization (WHO) guidelines, published in 2020, recommend a ferritin cut-off of less than 70 µg/L for individuals with inflammation or infection.

Total iron-binding capacity (TIBC)

The transferrin saturation is the amount of iron that is bound to transferrin, expressed as a percentage of the TIBC. In IDA (Iron deficiency anaemia), TIBC increases. Hepcidin binds to ferroportin (the iron exporter on cells) which reduces iron release from cells. Failure of release of iron from the ferritin stores results in a low TIBC. [6]

Transferrin and TSAT: Assessing Iron Transport

Transferrin: This protein transports iron in the blood. High levels of transferrin can suggest iron deficiency, as the body attempts to compensate for low iron levels by producing more transferrin.

Transferrin Saturation (TSAT): This measure indicates the proportion of transferrin that is bound to iron. A low TSAT suggests that iron is not readily available for use by the body.

In summary serum ferritin correlates with iron stores without the presence of inflammatory conditions; and TSAT determines the available iron for erythropoiesis.

Reticulocyte Hemoglobin Content: A Measure of Iron Utilization

This test measures the amount of hemoglobin in young red blood cells. A decrease in reticulocyte hemoglobin content

can indicate that the body is not efficiently using iron to produce red blood cells. An increase in reticulocyte hemoglobin content after iron treatment is a positive sign that the body is responding to iron therapy.

Emerging Markers Of Iron Status

In addition to ferritin and TSAT, newer markers are being explored to improve the accuracy of iron status assessment:

Hepcidin: A hormone that regulates iron absorption.

Soluble Transferrin Receptor: A marker of iron deficiency. Measurement of soluble transferrin receptor is more reliable at identifying IDA than TIBC and iron, but it is not widely available.[2,6]

Erythroferrone: A hormone that influences iron metabolism. These emerging markers may provide more precise insights into iron status, especially in complex clinical situations.

MCV and MCH:

Commonly used laboratory automated analyzers calculate MCV (hematocrit / RBC) and MCH (hemoglobin level / RBC) based on the measured parameters (RBC, hematocrit, and hemoglobin levels). Previous generations of laboratory analyzers used MCV directly for measurements, and IDA was defined as anemia with low MCV, or microcytic anemia. Red blood cells in IDA are characterized by reduced cell volume and decreased hemoglobin concentration, generally called hypochromasia. Provided that there is no double pathology including associated severe mechanical intravasular injury or hemolysis, RBC hemoglobin concentration is constant during the RBC lifespan. All these highlights the role of MCH, and IDA can be characterized by a hypochromic feature rather than a microcytic phenotype.[7]

Iron-refractory Iron Deficiency Anemia (IRIDA)

Iron-refractory iron deficiency anemia (IRIDA) is an inherited disorder of systemic iron balance in which both absorption and utilization of iron are impaired. IRIDA is rare recessive disease caused by mutations in general TMPRSS6 (Transmembrane serine protease TMPRSS6 also called matriptase 2). The disorder is refractory to iron administration, because high hepcidin levels prevent adequate iron absorption. The IRIDA is considered as the most "frequent" iron-related inherited anemia.[2,8]

Prevention

Primary Prevention

The primary prevention of iron deficiency anemia in infants and toddlers hinges on healthy feeding practices. In infants, the introduction of cow's milk in the first year of life is the greatest dietary risk factor for the development of iron deficiency and iron deficiency anemia. Cow's milk is low in iron, and its iron is poorly absorbed. In addition, it decreases the absorption of iron from other dietary sources. Therefore, the strict avoidance of cow's milk in the first 12 months of life is essential in preventing iron deficiency anemia.

Breastfeeding is the ideal feeding practice for many well-documented reasons, including lowering the risk of iron deficiency anemia. Although breast milk is low in iron content, about 50 percent of the iron is bioavailable to the infant. Yet, exclusive breastfeeding after four to six months puts infants at risk for iron deficiency. Therefore, some form of dietary iron supplement that provides 1 mg elemental iron per kg per day is recommended for term infants starting at four to six months of age.

Infants started on formula at birth and those switched from breast milk to formula should receive iron-fortified formula. Term and preterm infants (weighing more than 1,000 g) who are fed iron-fortified formulas are able to maintain iron sufficiency without additional iron supplementation.

Other preventive measures for toddlers include encouraging a diversified diet rich in sources of iron and vitamin C, continuing use of cereals fortified with iron instead of more advertised cereals, avoiding excessive juice intake.[9]

WHO has recognized food fortification as a potential universal tool for defeating IDA worldwide. A new approach for fortification of drinking water is presented for combating iron deficiency anemia worldwide. The idea is to leach Fe from a bed containing granular metallic iron (Fe0), primarily using ascorbic acid (AA). Calculated amounts of the FeII-AA solution can be added daily to the drinking water of households or day-care centers for children and adults (e.g. hospitals, kindergartens/schools, refugee camps) to cover the Fe needs of the populations. Fe fortification of safe drinking water is a practicable, affordable and efficient method for reducing IDA in low-income communities.[10]

Nutrition education: Community-centered, culturally sustainable nutrition intervention program can be helpful.[5]

Secondary Prevention

Infants with one or more risk factors should be screened for iron deficiency. The serum ferritin level, transferrin saturation, and erythrocyte protoporphyrin, Red-cell distribution width (RDW), hemoglobin measurement, complete blood count (CBC) with red blood cell indexes can be considered. It should be noted that elevated erythrocyte protoporphyrin level is not as specific for iron deficiency as other markers but elevated RDW is believed to be an early indicator of iron deficiency.[9]

CONCLUSION

Iron metabolism plays a crucial role in maintaining optimal bodily functions. Understanding the complexities of iron metabolism, distribution, and regulation is essential for early diagnosis and effective primary prevention of iron deficiency anemia (IDA). IDA is a widespread nutritional disorder affecting individuals worldwide, particularly those with high iron requirements. Early detection through serum ferritin, transferrin saturation, and emerging markers like hepcidin and erythroferrone is vital. Prevention strategies include promoting healthy feeding practices, iron-fortified foods and drinks, and nutrition education. Secondary prevention involves screening high-risk individuals and monitoring iron status. Effective management of IDA requires a multifaceted approach, incorporating dietary interventions, supplementation, and education to mitigate its adverse effects on cognitive function, physical performance, and overall well-being.

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